IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Art Unit: 1644
KALTOFT, et al.	)	Examiner: SAUNDERS, D.
Serial No.: 09/720,371	)	Washington, D.C.
Filed: April 30, 2001	)	September 21, 2004
For: METHODS OF EXPANDING AND SELECTING DISEASE ASSOCIATED T-CELLS	)	Docket No.: KALTOFT=1
	)	Confirmation No.: 2534

SUPPLEMENTAL RESPONSE AFTER RCE

U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, Mail Stop RCE
Crystal Plaza Two, Lobby, Room 1B03
Arlington, Virginia 22202

S i r :

On July 26, 2004, we filed an RCE requesting entry of the June 9 amendment.

We have additional comments to make in response to the July 19 advisory action.

The examiner is of the opinion that the statement in Flyer et al., in column 14, lines 59-63, anticipates the present invention. The examiner appears to have misunderstood the paragraph in column 14, lines 55-67, which provides a definition of the 'cell line' of mammalian origin that is used in the modified REM provided by Flyer.

According to Flyer's invention of a modified REM method, a (non-dividing) mammalian 'cell line', expressing at least one T-cell-stimulatory component, is added to the culture medium that is used to rapidly expand an initial T lymphocyte population (column 8, lines 16-22). Cell lines suitable for practicing 'modified REM' include mammalian cell lines expressing F-C-γ receptors (column 24, l. 41 - column 25, l. 3). Such cell lines may be obtained from two sources (column 25, l. 12-17):

- tumour cell lines that are demonstrated to express F-c-γ receptors (such as K562, HL60 and U937); or
- FcγR-positive cells lines obtained by immortalizing cells that already express F-c-γ receptors, e.g., viruses can be used to immortalize mammalian (including human) cells. Such virally immortalized cell lines are, by definition, not normal human cell lines.

Thus the mammalian cell lines that are provided by Flyer to practice his invention share a common property, namely they are leukemic (tumour) cell lines, which are **not derived from normal human (T) cell lines**. Indeed Flyer makes it clear that the mammalian 'cell line' to be used (column 14, l. 55 - column 15, l. 2), is not a population of cells that are not 'primary cells' taken from an individual, nor is it a PBMC mixed cell population. Rather the mammalian 'cell line' is derived from a tumour cell line as shown in Example 2, and it is well known that such tumour cell lines can often be cultured as immortal cell lines for many generations (Flyer, column 14, l. 59-63), while normal cell lines have a finite life span. In contrast, the T cells to be propagated, according to Flyer et al., are often derived from peripheral blood mononuclear cells (PBMC). According to Flyer's definition, T cells within the PBMC are not a "mammalian cell line" (column 14, l. 67 - column 15, l. 2). (We don't contend that Flyer's definition is in accordance with the usual scientific definition.)

'Cell lines' like K562, HL60 and U937 are, according to the claims in Flyer et al., so-called REM cell lines. As stated above, such (REM) cell lines are used to activate T cells to grow faster. Apparently the examiner seems (wrongly) to be of the opinion that the REM cell lines actually are the

T cell lines to be propagated. This is in part due to Flyer's new, but illogical definition of a REM cell line, because in the original REM patent (by Riddell) REM cell lines were/are the T cell lines propagated.

In the examples (and in the claims) according to Flyer et al., T cells can at best be expanded 1000 fold, that corresponds to 10 cell population doublings. This is far below the 10(9) to 10(10) cells (corresponding to 30-34 PD) that Riddell asserts can be obtained from a single T cell clone in the original REM patent. Flyer is aware of this fact (see column 7, l. 45-55).

Hence Flyer does not disclose the cytotoxic T cell line of the present invention which is derived from a normal T cell, and which has a life-span of at least 40 PD.

An anticipation rejection is based on a single reference. However, to properly interpret its teachings, the whole reference must be considered, not just bits and pieces taken out of context.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By: _____
Iver P. Cooper
Reg. No. 28,005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\g-i\HOFZ\Kaltoft 1\PTO SUPPLRESP AFTRCE.WPD